Claims 1-55 are pending in this application.

35 U.S.C. §112

Claim 48 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In particular, the Examiner objects to the recitation of "capable of hybridizing" as indefinite because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. Further, the Examiner objects to the recitation because it is not clear whether the recited set of probes have the potential to hybridize or do in fact hybridize the recited target nucleic acid which is to be detected. Applicants respectfully disagree with this rejection.

However, in order to expedite prosecution of the instant application, applicants have amended claim 48 to read "which hybridizes" in order to address the Examiner's concerns regarding this issue. Reconsideration and withdrawal of this §112 rejection is respectfully requested.

35 U.S.C. §102

Claims 22-27, 30-36, and 40-45 have been rejected under 35 U.S.C. §102(b) as being anticipated by Snitman, et al. (USPN: 5,641,630). Applicants respectfully disagree with this rejection.

The Examiner specifically points to Snitman, column 6, lines 46-51, as describing the use of unlabeled probe, where a "signal probe could be unlabeled" (Official Action- April 10, 2002; page 3, lines 18-19). Applicants respectfully disagree, as the indicated section does not mention that the signal probe could be unlabeled; rather, this section merely describes the requirements for the nucleic acid portion of the second probe.

Snitman teaches a method of detecting a target nucleic acid sequence from a solution employing two probes. The first probe serves as a capture probe, which is "covalently attached to a first complexing agent." The second probe serves as a signal probe, "which has a sequence complementary to a different selected portion of the target sequence than that which is complementary to the first probe, hybridizes to the target...[and a] detectable

reporter group is attached to the second probe sequence." (See Snitman, column 4, lines 45-57). The second probe is labeled or modified with a reporter group (col. 6, lines 52-67). In every embodiment, the second probe is modified for detection. No method of detecting the sandwich complex using an unmodified second probe is taught or suggested in this reference. Therefore, both probes, according to Snitman, must be labeled or modified.

Further, the Examiner asserts that Snitman describes "detecting the hybrid complex by binding an antibody which recognizes the hybrid (see col. 5, lines 43-67, col. 6, lines 1-6)". Applicants respectfully disagree with the Examiner's reading of this section of Snitman.

Applicants respectfully direct the Examiner's attention to the first paragraph of the Summary of the Invention (col. 4, lines 45-57). In this paragraph, the parts of the invention are identified and given names. Here, it describes that the Snitman invention relates to a method for detecting a target nucleic acid using a first and second probe. The first probe sequence is covalently attached to a first complexing agent, and the second probe sequence is attached to a detectable reporter group. In the next paragraph (col. 4, lines 58-67), Snitman explains that the first probe sequence is immobilized onto a solid support via an interaction between the covalently bound first complexing agent and a second complexing agent on the solid support. Therefore, the phrase "first complexing agent" relates to a moiety attached to the first probe which provides a means for immobilizing that probe onto a solid surface. With this background, the text in the section cited by the Examiner (col. 5, line 43 through col. 6, line 6) takes on new meaning. In the paragraph bridging columns 5 and 6, Snitman describes some details of the first probe, and its covalently-bound first complexing agent are provided. Here, it is described that the "first complexing agent," i.e. the moiety which allows immobilization onto the solid matrix, may be "an antigen, such as fluorescein or an antibody, such as anti-fluorescein." Snitman also exemplifies this embodiment in the examples, provided later in the specification, which use a fluorescein antibody-modified solid support to capture the fluorescein-labeled first probe. *See e.g.*, Example 1, col. 13, lines 56-58 and col. 14, lines 60-62; and Examples 2-6. Therefore, the Snitman specification does not teach or suggest the use of an antibody which recognizes the RNA:DNA hybrid as a means for detecting the complex.

Similarly, the Examiner refers to col. 6, lines 52-67 as describing that the "antibody could be labeled with alkaline phosphatase." Applicants respectfully disagree with this interpretation.

Keeping in mind the names given to the various parts of the invention described in the Summary of the Invention discussed above, it is clear that the "reporter group" discussed in the cited section, i.e. col. 6, lines 52-67, relates to labels which are attached to the second probe. These reporter groups are quite distinct from the "first complexing agents" discussed in the context of the use of antibodies. Nowhere in the Snitman reference is there any teaching or suggestion for the use of labeled antibodies as a means for detecting the complex.

As relates to claims 40-45, rejected by the Examiner in view of Snitman, these claims are directed to the use of an unmodified signal probe. Snitman does not teach or suggest the use of an unmodified "second probe." In fact, every embodiment of Snitman utilizes a labeled or modified probe, because this probe, in Snitman, serves as the direct detection means. No other means of detection is taught or suggested. Reconsideration and withdrawal of this 102(b) rejection of claims 40-45 is respectfully requested.

Regarding claims 22-27 and 30-36, these claims use a specific detection system which is not taught or suggested in Snitman. In particular, claims 22-27 and 30-36 detect the RNA:DNA complex through use of an antibody specific for RNA:DNA complexes. This detection system is not taught or suggested in Snitman. Reconsideration and withdrawal of this§102(b) rejection of claims 22-27 and 30-36 is respectfully requested.

35 U.S.C. §103

Claims 1-6, 10-12, 15-26, 30-38, 40-46, 48, 50-51, and 53-55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Snitman, et al. (USPN: 5,641,630) and in view of Collins, et al. (USPN: 6,232,462) and Shah, et al. (USPN: 5,629,156). Applicants respectfully disagree with this 103(a) rejection.

As an initial matter, applicants respectfully point out that claims 22-26, 30-31, 33-36, and 40-45, which have been rejected over Snitman in view of Collins and Shah, do not relate to the use of blocker probes. Therefore, applicants assume that these claims were erroneously included in the §103 rejection, because this combination of references does not relate to the claimed subject matter. Further applicants believe the deficiencies in the Snitman reference discussed above, are not remedied by the Collins and Shah references as the references relate to claims 22-26, 30, 31, 33-36, and 40-45. Reconsideration and withdrawal is respectfully requested.

Regarding the rejection to claims 1-6, 10-12, 15-21, 32, 37-38, 46, 48, 50-51, and 53-55, which are directed to using blocker probes, applicants assert that the Snitman reference does not teach or suggest the claimed method of detecting a target nucleic acid using blocker probes. In fact, the Examiner readily admits that the primary reference (i.e. Snitman, et al.) does not teach or suggest the use of blocker probes as claimed. The Examiner then combines Snitman with the Collins, et al. and Shah, et al. references.

The Collins reference at col. 9, lines 33-67, col. 10, lines 1-17, and col. 23, lines 53-67, as cited by the Examiner, relates to the use of "capture extender molecules." The Examiner equates these to the blocker probes of the present invention. Applicants respectfully disagree with this interpretation of the Collins reference.

The use of capture extenders (or "CEs") in Collins is illustrated in Figure 1. In this figure, it is clear that these CEs are not acting as blocker probes, i.e. hybridizing to excess non-hybridized capture sequence probes, but rather are acting as a component in the target nucleic acid complex. The CEs act as a bridge between the capture probe and the target, but not as a means for removing or binding up excess non-hybridized capture sequence. Therefore, Collins, as cited by the Examiner, does not teach or suggest blocker probes as claimed.

The Shah reference describes a method of capture-release, where a target is hybridized with a first capture probe and a detector probe at two different regions of the target molecule, where the capture probe is used to bind the resulting complex to a solid support. After target capture, the target is released from the first solid support under conditions where the first capture probe remains bound to the solid surface since it has a higher affinity for the solid support than the target, and the detector probe remains bound to the target. The target detector probe complex is then exposed to a second capture probe which forms a new complex with the target (see col. 4, line 5). This function requires that the second capture probe is complementary to the target sequence. In contrast the blocker probes of the claimed methods are not complementary to the target, but rather contain sequence which is IDENTICAL to the target nucleic acid. See Figure 2 of the instant specification. Such probes are not taught or suggested in the Shah reference. Conversely, the second capture probes, which the Examiner equates with blocker probes, could not be used in the present invention because those probes would not "hybridize to the excess non-hybridized capture sequence probes" as required by the instant claims. Shah specifically points this out in his

description on Col. 7, line 22, where it states that the second capture probe has "no affinity for the first capture probe." Therefore, Shah does not teach or suggest the blocker probes as used in the claimed methods.

The combination of Snitman, Collins, and Shah fails to make the present invention obvious. Snitman fails to teach or suggest an assay using (1) an unmodified signal probe; (2) an RNA:DNA antibody as a means for detection; or (3) a blocker probe of any kind. Collins and Shah do not remedy these deficiencies. In particular, the Examiner asserts that Collin's "capture extenders" are, in effect, blocker probes. However, in fact, the capture extenders do not hybridize to excess non-hybridized capture probes, but rather act as bridging probes between the capture probe and target. Shah also does not teach or suggest blocker probes because the analogous probe (i.e., the second capture probe) has no affinity for the first capture probes, which is a required function of the blocker probes of the present invention. Therefore, none of the references, alone or when viewed in combination, teach or suggest the blocker probes of the claimed method or the claimed method as a whole. Therefore, in reading the cited references, the skilled artisan would not be able to generate the claimed method, which uses blocker probes for preventing non-specific hybridization of capture oligonucleotides to a target. None of the references, even when viewed in combination teach or suggest the use of these blocker probes. Thus, applicants respectfully request reconsideration and withdrawal of the §103(a) rejection.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

As required by 37 C.F.R. 1.121, a marked up version of the replacement claims is provided and attached hereto.

The Commissioner is hereby authorized to charge any additional fees which may be required for the timely consideration of this amendment under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4017.

Respectfully submitted,
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Dated: July 9, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend the claims as follows:

40. (twice amended) A method of detecting a target nucleic acid comprising:

a) hybridizing a single stranded target nucleic acid to a capture sequence probe and a signal sequence probe, wherein the capture sequence probe and the signal sequence probe hybridize to non-overlapping regions within the target nucleic acid and do not hybridize to non-overlapping regions within the target nucleic acid and do not hybridize to each other, wherein the signal sequence probe is unlabeled and comprises a DNA-RNA hybrid region, wherein said hybridization forms a complex; and

b) detecting said complex.

48. (amended) The method according to claim 1, wherein the signal sequence probe comprises a DNA-RNA duplex and a single stranded nucleic acid sequence which [is capable of hybridizing] hybridizes to the target nucleic acid.